



The Biologics License Application Process

An Overview

3/31/2004



Preface

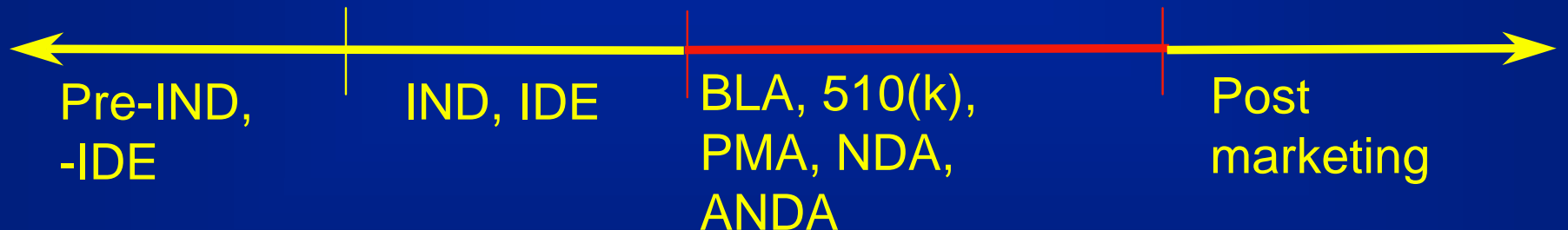
- **This presentation walks through the review process for a BLA.**
- **CBER reviews and approves/clears medical devices (510(k) and PMA) as well as new drugs (NDA and ANDAs)**
- **Please bear in mind that the principles presented here are generally applied to these other regulatory pathways (with adjustments to accommodate their specific regulatory requirements/recommendations)**
- **For example....**



Drug development phases:



Review submission types:



What is a Biologics License Application (BLA)?

A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

21 CFR 601.2



CDER Regulatory Authority

- **BIOLOGICS**

- Investigational New Drug Exemptions (IND, 21 CFR 312)
- Biologics License Applications (BLA, 21 CFR 600-680)

- **EXAMPLES**

- Vaccines and allergenic products
- Blood Products (including blood grouping reagents and donor screening tests for bloodborne pathogens)
- Cellular & gene therapies, xenotransplantation)



Who Submits a BLA ?

MANUFACTURER (Applicant)

- Any legal person or entity who is engaged in manufacture

or

- An applicant for a license who takes responsibility for compliance with product and establishment standards



What is in a BLA?

- **Form FDA 356h (cover sheet)**
- **Applicant Information**
- **Product / Manufacturing information**
- **Pre-clinical studies**
- **Clinical studies**
- **Labeling**



BLA – Applicant Information

- **Name, address & phone number**
- **Name & address of facilities**
- **Authorized official**



BLA – Product/Manufacturing Information

- **Source material / raw materials**
- **Manufacturing process and controls**
- **Formulation**
- **Facility information**
- **Contamination/cross-contamination information**
- **Environmental assessment or categorical exclusion**



BLA – Safety, Efficacy and Use Information

- **Pre-clinical studies**
- **Clinical studies**
- **Labeling**



International Harmonization

Using the CTD (Common Technical Document)

- An agreed upon common format for the modular presentation of summaries, reports and data
- Content is harmonized to the extent of relevant ICH guidelines
- Guidance for Industry:
Submitting Marketing Applications According to the ICH-CTD Format - General Considerations
 - <http://www.fda.gov/cber/gdlns/mrktapich.pdf>



Electronic Submissions

- Submission of BLA/S may be made on paper or electronically
- Submissions should be made in accordance with published guidance:
 - <http://www.fda.gov/cber/esub/esub.htm>



Managed Review Process

● MRP

- Developed to meet PDUFA requirements
- Standardized the review process
- Helps standardize review content (scientific review)
 - Not all review content can be standardized
 - Product variation
 - Manufacturing process variation
 - Complexity of biologics
 - Some review content can be standardized
 - Where the knowledge base is sufficient for
 - products
 - processes



Managed Review Process

- **Milestones in the review process are “positive” or “negative” actions, e.g.,**
 - IND/IDE hold/disapproval (Negative)
 - BLA, PMA, etc., Refuse to File (Negative)
 - Issue an approval (Positive)
- **These decisions are based on review of the submission by the review team**



The Review Committee

**CONSTITUTED TO CONTAIN THE
NECESSARY EXPERTISE TO
REVIEW THE SUBMISSION**



Responsibilities – Chairperson/Lead

- **CONSTITUTE** the committee
- **ASSIGN** sections for review
- **SCHEDULE** and **CONDUCT** meetings w/RPM
- **REVIEW** according to Managed Review and Good Review Management Principles
- **WRITE** “action” letters w/RPM
- **PRESENT** at Advisory Committee Meetings
- **REQUEST** a pre-license inspection
- **PREPARE** a Summary of Basis for Approval (SBA)



Responsibilities Regulatory Project Manager

- **MANAGE** the review of the application
- **REVIEW** assigned portions of application
- **PERFORM** QC check on the review process
- **ASSURE** reviews are documented properly
- **ASSURE** review of labeling is complete
- **COORDINATE** compliance status check
- **PREPARE** approval letter for new products
- **PREPARE** finding of no significant impact



Responsibilities Discipline Reviewer

- **REVIEW** assigned sections of the application
- **WRITE** a review memo, containing a summary, recommendation for action and letter-ready questions
- **ATTEND** and **PARTICIPATE** in review committee meetings following Good Review Management Principles and Managed Review Procedures
- **COMMUNICATE** with the applicant and document the discussion (as per Staff Manual Guide 2126.2)
- **PREPARE** for Advisory Committee meetings
- **PARTICIPATE** in the pre-approval inspection (if necessary)
- **CONSIDER** if a public health and/or research questions need to be answered relative to product approval



Before the BLA is Submitted

- **Pre-BLA meeting**
 - **CBER SOPP 8101.1 Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants**
- **Identify potential review committee**
- **Consider Advisory Committee needs & schedule**
- **Arrange for BiMo Inspection**



Application Received

- **Administrative processing**
 - Submission tracking number assigned (STN)
 - data entry
 - user fee verification
- **First committee meeting**
 - review assignments
 - time frames



SUBMISSION TRACKING NUMBER
aaaaaa.bbbb/cccc



Filing Review

- **Review for completeness**
 - RTF policy
 - CBER SOPP 8404 Refusal to File Guidance for Product License Applications and Establishment License Applications
- **Filing meeting**
- **Filing letter**
- **Communicate any significant deficiencies noted up to that time (but not a complete review) by day 74**



Refuse To File

- A refusal to file (RTF) letter is issued when the submission has been deemed not sufficiently complete for a meaningful review
- 21 CFR601.2(a), RTF Policy, SOPP 8404
- The Applicant may request that the submission be Filed Over Protest: SOPP 8404.1



CBER Management Oversight: QA

- **Refuse to File Oversight Committee**

- **Composed of representatives from**

- CBER Management (Review Management, Policy, QA, Deputy Director for Medicine, Center Director)
 - Product Offices (OBRR, OVRR, OTRR, OCBQ)
 - Center for Drugs (Office of Medical Products)

- **Review team presents a summary highlighting the reason for the refusal to file**
 - **The Applicant is invited to present their point of view**
 - **Evaluates the quality of the review process**



Complete Review

- **Substantive review**
 - Information requests
 - Discipline reviews
 - Review memos
 - Labeling
 - Lot release protocols
- **Inspections**
 - Facility
 - Bioresearch Monitoring
- **Advisory Committee presentation, as appropriate**



Information Requests (IRs)

- Issued while the review is in progress
- Requests information needed to continue the review
- IRs may be made by letter, telephone or FAX
- IRs are documented in the file
- The response to an information request should not be so great as to constitute a major amendment
- Responses to information requests do not necessarily have to be reviewed in the current review cycle
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1



Discipline Reviews (DRs)

- A DR letter is issued when a particular discipline (clinical, CMC, etc.) has finished its review, but the complete review is not yet done
- A DR letter contains comments and questions that might appear in the action letter
- Responses to DR letters need not necessarily be reviewed prior to issuance of the action letter
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1



Administrative Record

- Paper trail documenting the decision making process and basis for the decision
- Copies of Telecons, FAXes, Review Memos, Meeting Minutes, etc., become part of the administrative record and are entered into the file and the tracking system



Action Decision

- **After a complete review is finished**
 - Inspections
 - Advisory Committee
- **Review Committee meeting**
 - Outstanding issues
 - Agreements & commitments
- **License action recommendation**
 - Not ready for approval
 - Approval



ACTION

Not Ready for Approval

- **COMPLETE RESPONSE LETTER**

- Itemizes all deficiencies in the application that must be corrected prior to approval
- Stops the review clock

- **RESUBMISSION**

- Class 1 or 2
- Restarts the clock



PDUFA Resubmissions

- **Guidance for Industry: Classifying Resubmissions in Response to Action Letters, May 14, 1998**
- **SOPP 8405.1 Procedures for the Classification of Resubmissions of an Application for a Product Covered by PDUFA III**



Performance Goals (con't)

Resubmitted Applications (Efficacy Supplements)

- **Class 1**
 - 90% in 2 months (90% in 4 mo.; 50 % in 2 mo.)
- **Class 2**
 - 90% in 6 months (90% in 6 mo.)
- **Clinical Hold Responses**
 - 90% in 30 days
- **Major Dispute Resolution**
 - 90% in 30 days
- **Special Protocol Assessments**
 - 90% in 45 days



Dispute Resolution

- **Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level**
- **SOPP 8005 Major Dispute Resolution Process (2/11/99)**



ACTION

Approval

- **Compliance check**
- **Summary of Basis for Approval (SBA)**
- **Finding of No Significant Impact (FONSI) or confirm categorical exclusion**
- **Approval letter**
 - **Grants permission to distribute**
 - **Itemizes all agreements & commitments**
- **Issue license**



Rules of the Road for Reviewers

- **SGRA**

- **SOPPs**

- **Guidances**

- **Regulations**

- **Acts**



Good Review Management Principles

Addendum



Good Review Management Principles

- **Guidance issued under PUDFA III**
- **To promote improving review performance in the first cycle by focusing on**
 - **FDA activities**
 - **Sponsor activities**
 - **Communications**
 - **At each stage of the review....**



Good Review Management Principles

- **Presubmission**
- **Application Receipt Processing (Prefiling)**
- **Filing**
- **Review Planning**
- **Review**
- **Advisory Committee Meetings**
- **Wrap Up and Labeling**
- **Action**
- **Cycles of Review**



Good Review Management Principles

- **Overall Principles - FDA Focus**

- **Ensure a well managed review**
 - A.** A strong interdependence among the primary FDA review team,
 - B.** frequent interactions between the primary review team and supervisory reviewers, and
 - C.** and project management is critical in the successful completion of the first-cycle review,
 - D.** all which helps FDA staff to accommodate unanticipated events or findings that may develop during the course of the review, using fewer resources in resolution of the issues and preventing the need for crisis management - which is inefficient and often error-prone - to meet PDUFA goals.
- **Solve readily correctable problems within the first cycle**
- **Timely notification of significant deficiencies**



Good Review Management Principles

- **Overall Principles - Applicant Focus**
 - **Provides a complete application upon initial submission**
 - A. all required and expected information to support approval of the requested claims, labeling, and dosage forms
 - B. application is submitted in a readable, well-organized format
 - **The applicant is strongly encouraged to manage the drug development timeline in a manner that leads to submission of a complete application, with the exception of safety updates, for FDA review**



Good Review Management Principles

- **Overall Principles - Communications between FDA and the Applicant**
 - A.** The Agency believes that open communication of advice, guidance, and notification of deficiencies should occur at pivotal points during the drug development and review process (e.g., the end-of-phase 2 meeting, the pre-NDA/BLA meeting, and during the filing review) and on an as-needed basis.
 - B.** To ensure consistent communication, it is recommended that the FDA and applicants follow the general guidelines discussed in the following sections as they pertain to each phase of the first-cycle review process.

